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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/020,541	04/26/2002	Larry A. Wheeler	17400(BAR)	1687

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/020,541	WHEELER ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,18-22 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,18-22 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 4/3/2006.

The amendment filed 4/3/2006 is acknowledged and has been entered.

Claims 16, 18-22 and 30 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 16, 18-22 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Application publication No US 2002/0040015 A1 (Miller at al.) in view of U.S.

Patent No. 6,180,402 B1 (Granville et al.) and further in view of Wheeler et al. (Europ. Jour. Ophthal., JAN-MAR 1999) for the reasons of record set forth in the Office Action mailed on 1/19/2006 and reproduced below for convenience.

It is noted that the effective filing date of the Miller reference, with respect to PDT in combination with an anti-angiogenic agent is 2/10/2000.

Miller teaches a method and composition for treating conditions of the eye. Specifically, Miller teaches a method for photodynamic therapy (PDT) of ocular conditions characterized by the presence of unwanted choroidal neovasculature which includes enhancing the PDT method by administering an antiangiogenic compound (e.g., see abstract; paragraph 18; claims 20-31, etc.). It is noted that the instant specification acknowledges it was previously known that PDT can result in optic nerve atrophy (See p. 3, first paragraph).

Miller does not teach that the method includes the administration of the anti-apoptotic compound Brimonidine.

Granville teaches that it is beneficial to include an anti-apoptotic molecule in PDT treatments in order to ameliorate the adverse effects of PDT (e.g., see column 6, lines 46-64; column 8, lines 52-63; column 10, lines 15-50; column 11, lines 26-46; column 12, lines 15-20; claim 1; etc.). Specifically, Granville teaches a method of PDT treatment wherein an anti-apoptotic agent is used with the PDT treatment, and teaches that the PDT treatment can be for treating conditions of the eye (e.g., see 11, lines 26-65; column 9, lines 8-15; column 10. lines 15-25; etc.)

Granville does not teach that the anti-apoptotic molecule can be brimonidine.

Wheeler teaches that Brimonidine is an alpha-2 agonist compound that is an anti-apoptotic neuroprotective agent that can inhibit apoptosis and protect ocular neural tissue as demonstrated in animal models of retinal and optic nerve injury (e.g., see page S20, second column; page S21, etc.).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to perform the method taught by Miller and to include an anti-apoptotic molecule in the treatment (as taught by Granville) and to use Brimonidine as the anti-apoptotic agent with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to use an anti-apoptotic agent in the PDT treatment because Granville teaches that it is beneficial to include an anti-apoptotic molecule in PDT treatments in order to ameliorate the adverse effects of PDT. Furthermore, one of ordinary skill in the art would have been motivated to use Brimonidine as the anti-apoptotic agent because Wheeler teaches that Brimonidine is an anti-apoptotic agent that can be used to protect target cells from neuronal injury (e.g., see page S20-S21, etc.), thus Brimonidine is an art recognized equivalent of the anti-apoptotic agents taught by Granville (see MPEP 2144.06-2144.07 regarding substitution of equivalents).

Response to Arguments

Applicant's arguments with respect to the rejection of claims under 35 U.S.C. § 112, second paragraph, (see page of the communication filed on 4/3/2006) have been fully considered and are persuasive; therefore, the rejection has been withdrawn.

With respect to the rejection of claims under 35 U.S.C. § 103(a), Applicant's arguments filed 4/3/2006 (see pages 4-11) have been fully considered, but they are not persuasive.

Applicants' assert that in order to establish a *prima facie* case of obviousness the Office must provide evidence of a suggestion or motivation to modify or combine the reference teachings, a skilled artisan would have had a reasonable expectation of success if the suggestion were followed, all of the claim limitations must be taught or suggested by the prior art references, hindsight reconstruction of the claim to find obviousness is always improper, and the invention must be considered as a whole (see page 5 of the 4/3/2006 communication).

The Examiner acknowledges Applicants assertion regarding the establishment of a prima facie case of obviousness, and does not take issue with Applicants assertion. Applicants are respectfully reminded, however, that it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Furthermore, when considering the state of the art *as a whole,* there is a suggestion or motivation to combine the reference teachings (which teaches all of the claim limitations) and one of ordinary skill in the art would have had a *reasonable* expectation of success.

Applicants have responded to the rejection of claims under 35 U.S.C. § 103(a) by attacking the references individually. For instance, in the response filed 4/3/2006, Applicants attack the Miller et al. reference (U.S. Patent Application No. 2002/0040015) on pages 6-7, the

Granville et al. reference (U.S. Patent No. 6,180,402) on pages 8-9, and the Wheeler et al. reference (Eur. J. Opthal., 1999) on pages 9-11.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, Miller et al. teaches the general state of the art with respect to photodynamic therapy (PDT) to treat conditions of the eye, including choroidal neovascularization using PDT in combination with an antiangiogenic factor. Miller, however, is silent with respect to using agents to ameliorate adverse side effects of PDT. Granville et al. teaches that it is beneficial to include an anti-apoptotic molecule in PDT treatments in order to ameliorate the adverse effects of PDT or to enhance the selectivity of PDT. Wheeler teaches that Brimonidine is an anti-apoptotic neuroprotective agent that can inhibit apoptosis and protect ocular neural. It was also known (and the instant specification acknowledges on page 3, first paragraph) that PDT can result in optic nerve atrophy. Therefore, considering what was known in the art, *as a whole*, it would have been *prima facie* obvious to one of ordinary skill in the art, at the time of filing, to combine the cited references to make the claimed invention with a reasonable expectation of success.

With respect to the Miller et al. reference, Applicants argue that the use of the Miller reference is improper because in order for the Miller reference to be considered prior art, it must rely on the disclosure of the provisional application to which it claims priority (U.S. provisional application 60/181,641, hereafter "the '641 provisional application") and when considering the entire teaching of the provisional application the reference allegedly teaches away from using an

anti-apoptotic molecule in conjunction with PDT (see pages 6-7 of the 4/3/06 response). Applicants argue that the '641 provisional application contains disclosure concerning the use of modulators of apoptosis in conjunction with PDT and, applicants assert, specifically teaches the use of an apoptosis inducing factor in conjunction with PDT (see page 7 of the 4/3/06 response). Applicants contend that the '641 provisional application teaches away from using an anti-apoptotic agent in conjunction with PDT and provides no motivation for using PDT in conjunction with a neuroprotectant such as brimonidine, as is claimed.

In response, it is acknowledged that the '641 provisional application does not teach using an anti-apoptotic molecule (such as the neuroprotectant brimonidine) in conjunction with PDT. However, the Examiner respectfully disagrees with Applicants contention that the '641 provisional application teaches away from using an anti-apoptotic molecule such as the neuroprotectant brimonidine in conjunction with PDT because: (1) the '641 provisional application is silent with respect to using an anti-apoptotic agent as a neuroprotectant; and, (2) the '641 provisional application only contemplates using a pro-apoptotic agent to enhance the cytotoxic effect of PDT specifically in the target neovasculature (see the specific passages of the '641 application cited by the applicants on page 7 of the 4/3/06 response). It is the Examiner's position that teaching the use of an apoptosis-inducing agent in conjunction with PDT in order to enhance the cytotoxic effects of the PDT in neovasculature tissue does not teach away from using PDT in conjunction with an anti-apoptotic agent wherein the anti-apoptotic agent is used as an agent to protect the non-target tissue, such as the neural tissue, which could be damaged by PDT treatment.

With respect to the Granville et al. reference, Applicants acknowledge that Granville et al. teaches PDT in conjunction with an anti-apoptotic agent (see page 8, first paragraph of the 4/3/06 response). However, Applicants argue that Granville et al. teaches that some agents may be apoptosis-inhibitors in certain cell types and apoptosis-inducers in other cell types. Applicants argue that Granville et al. only discloses using an anti-apoptotic agent in blood cells and does not disclose or suggest the use of neuroprotectants such as brimonidine. Applicants also assert that it is not clear whether the anti-apoptotic agents disclosed by Granville et al. would stimulate or inhibit apoptosis in neural cells. Applicants contend that the combination of Granville et al. and the Miller et al. provisional application reflect opposing teachings and indicate confusion in the state of the art at the time of filing (see pages 8-9 of the 4/3/06 response). Applicants argue that neuroprotection is not mentioned or suggested in either the Miller provisional application or in Granville. Applicants also contend that the references make clear that there are a myriad of different ideas about how to improve the efficacy of PDT including induction of apoptosis and inhibition of apoptosis.

In response, it is acknowledged that Granville et al. teaches that some agents may be apoptosis-inhibitors in certain cell types and apoptosis-inducers in other cell types. However, it is respectfully pointed out that brimonidine was taught in the prior art to be an anti-apoptotic neuroprotectant (see Wheeler et al., cited in the rejection). Therefore, regardless if the agents disclosed by Granville et al. stimulate or inhibit apoptosis in neural cells, the prior art teaches that brimonidine is an anti-apoptotic neuroprotecting agent. Furthermore, Granville et al. specifically teaches that the anti-apoptotic agent that is used in conjunction with PDT is useful for ameliorating the side effects and for enhancing the selectivity of PDT (e.g., see abstract of

Granville et al.). Granville et al. also specifically teaches administration of the agents to the eye (as previously indicated, see above). Furthermore, since Miller et al. teaches that an apoptotic-inducing agent can be used to enhance the cytotoxicity of PDT, and considering that Granville et al. teaches that an anti-apoptotic agent can ameliorate the side effects and enhance the selectivity of PDT, the Miller and Granville references are not in conflict and do not reflect confusion in the state of the art at the time of filing. The Examiner respectfully disagrees with Applicants argument that neuroprotection is not mentioned or suggested in either the Miller provisional application or in Granville. It is respectfully pointed out that the Miller provisional application explicitly teaches,

> "The anti-angiogenesis factor can potentiate the cytotoxity of the PDT. The potentiation may result in enhanced occlusion of the choroidal neovasculature. In addition, the anti-angiogenesis factor can enhance the selectivity of photodynamic therapy, for example, by permitting occlusion of the choroidal neovasculature while at the same sparring surrounding blood vessels, for example, normal choroidal vasculature, and/or tissue, for example, the overlaying neurosensory retina." (See page 3)

Therefore, the Miller provisional application does mention, "sparring... the overlaying neurosensory retina" which not only suggests, but actually teaches that neuroprotection in PDT is desired. Furthermore, it is noted that one of ordinary skill in the art would know that that PDT can result in damage to neural tissue including optic nerve atrophy, as acknowledged in the instant specification (see p. 3, first paragraph). Furthermore, one of ordinary skill in the art would also certainly understand that ameliorating the PDT damage to neural tissue such as the neurosensory retina and optic nerve would be desirable.

With respect to the Wheeler et al. reference, Applicants argue that without the knowledge of the instant specification or the post-filing art, one of ordinary skill in the art could not have had a reasonable expectation of success in the use of Brimonidine, which, Applicants point out,

is not mentioned in either the Miller or Granville references. Applicants also point out that Wheeler does not mention using brimonidine or other neuroprotectants in PDT. Applicants also argue that brimonidine is not an art recognized equivalent of the anti-apoptotic agents taught by Granville because Granville teaches the use of protease inhibitors while brimonidine appears to act by enhancing neuron-specific intrinsic signaling pathways that are selectively mediated by the alpha 2 adrenergic receptor. Applicants also cite M.P.E.P. 2144.06 statement "in order to rely on equivalence as a rational supporting an obviousness rejection, the equivalency must be recognized in the art and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents." (Emphasis is Applicants). Applicants contend that it is neither legally or scientifically obvious that this effect (employing the biochemistry of the target cells themselves to survive apoptotic signaling) would function in PDT, being a wholly different means of inhibiting apoptosis than described in Granville. Applicants argue that, at the very most (and despite the lack of any suggesting in Miller or Granville), a person of skill in the art might be curious as to whether brimonidine would be useful in PDT therapy, but that such a person could have had no reasonable expectation of success in satisfying this curiosity.

In response, it is acknowledged that none of the cited references teach using brimonidine in PDT. However, the lack of such a teaching does not negate the obviousness of using brimonidine as a neuroprotectant in conjunction with PDT. The Examiner respectfully disagrees with applicants argument that brimonidine is not an art-recognized equivalent of Granville's anti-apoptotic agent. In response to applicant's arguments, it is respectfully pointed out that Granville explicitly teaches,

"Agents that inhibit the expression of the oncogene cMyc or that cause the over-expression of the proto-oncogene bcl-2 can inhibit the induction of apoptosis." (Emphasis added, see column 3, lines 17-19);

and Wheeler explicitly teaches,

> "Examination of the mRNA expression in retinas using PCR revealed that brimonidine treatment induced an upregulation of the mRNAs for genes known to suppress the apoptotic program. Within 3 to 6 hours following brimonidine treatment, bcl-2 mRNA levels were elevated 2 to 3 fold over vehicle control-treated animal (data not shown)." (See page S20, second column; emphasis added).

Therefore, considering the Granville reference in its entirety, it is clear that Granville recognizes agents that cause over-expression of bcl-2 as inhibitors of apoptosis, and further considering that Wheeler teaches that brimonidine causes the over-expression of bcl-2, one of ordinary skill in the art would have recognized that the any agent that cause the over-expression of bcl-2, such as brimonidine, could be used as an agent to ameliorate the side effects of PDT (as taught by Granville). As such, brimonidine would be an art-recognized equivalent that could be used as the anti-apoptotic agent in the method taught by Granville. Therefore, Granville teaches employing the biochemistry of the target cells themselves (via bcl-2 over-expression) to survive apoptotic signaling. As such, and without evidence to the contrary, it would be legally and scientifically obvious that this effect would function in PDT.

Applicant's citation of M.P.E.P 2144.06 is acknowledged. It is respectfully pointed out that M.P.E.P. 2144.06 also states,

> "An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 32 (CCPA 1982)."

It is also respectfully pointed out that M.P.E.P. 2144.07 states,

> "The selection of a known material based on its suitability for its intended use supported prima facie obviousness determination in Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945)."

Based on the teaching of Granville that anti-apoptotic agents include agents that cause the over-expression of bcl-2 and the teaching of Wheeler that brimonidine causes over-expression of bcl-2, the Examiner believes that there would be a *reasonable* expectation that brimonidine could be successfully used in PDT therapy. Applicants are respectfully reminded that M.P.E.P. 2143.02 indicates that obviousness requires only a reasonable expectation of success.

Therefore, at the time of filing, the claimed invention would have been prima facie obvious to one of ordinary skill in the art in view of the teachings of the prior art as a whole. Furthermore, there would have been a reasonable expectation that combining the teachings of the prior art references to make the claimed method would be successful.

Accordingly, Applicants arguments with respect to the rejection of claims under 35 U.S.C. § 103(a) are not persuasive.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Art unit 1635